REMARKS

1. General Matters

1.1. Overview of Claim amendments

Claim 1 has been amended in several respects. The recited splice variant sequences no longer include SEQ ID NOs:96-103.

The phrase "is encoded by differential exon usage" was deleted for clarity purposes.

Limitations regarding the N-terminal flanking sequences were added. This amendment was performed in order to overcome the 35 USC §112 rejection, and is based on limitations previously included in claim 10 (which is now canceled), the information provided in pages 26-27 of the application and in the legend of figure 4 (page 12 of the application). Further details about this amendment are provided below.

The phrase "wherein said splice variant of an ErbB ligand exerts inhibitory activity on ErbB receptor-mediated signaling" was added. This amendment is based on a limitation previously included in claim 13 (which is now canceled).

Claim 5 has been amended to recite SEQ ID NOs. 93, 95, 104, 109 and 110).

Claim 14 has been rewritten to depend from claim 1 instead of claim 13 (which is now canceled).

Claims 8-10 and 13 have been canceled.

Claim 42 is new. Claim 42 parallels amended claim 1, but omits the latter's N-terminal flanking sequence limitation.

All new claims read on the elected invention.

1.2. Election/Restriction (OA pp. 2-4)

The only sequences specified in claim 1 are SEQ ID NOs. 74-84, 93, 95, 104, 109 and 110. These sequences share the specific features detailed in the claim.

Claim 1 as amended thus pertains to variants having a special technical relationship among them that unifies them in PCT practice. In this regard, please note the standard set forth in PCT Administrative Instructions, Annex B, paragraph (f) ("Markush practice").

The variants all share a common structure (i.e., a common "significant structural element", see Administrative Instructions (f)(i)(B)(1)), specifically, truncated EGF domain having only the first four (of six) conserved cysteines found in an intact EGF domain. The variants end one amino acid after the fourth conserved cysteine. The truncated EGF domain of the variants contains a consensus sequence that can be represented as follows: (X-8)-Cys-(X-7)-Cys-(X-2 to 3)-Gly-X-Cys-(X-10 to 13)-Cys-X, where X is any sequence of the relevant number of amino acids, e.g. "X-8" represents a sequence of any eight amino acids (please see page 35 lines 30-32 of the application).

The variants share a common function and effect (i.e., a common property and activity, see Administrative Instructions (f)(i)(A)) - they exert inhibitory activity on ErbB receptor-mediated signaling. As explained in the background section of the application (see pages 1-2), the four ErbB receptors are part of an interconnected signaling network, where ligand stimulation induces the formation of homo- and heterodimers between the different receptors. For two of the receptors, namely ErbB2 which has no known direct ligand and ErbB3 which lacks an intrinsic tyrosine kinase activity, heterodimers are the only functional form. The signaling cascade continues by recruiting downstream signaling molecules. One particular activating ligand is typically associated with more than one receptor and activates several different ErbB receptor complexes or combinations. Most activating ligands can induce

the formation and activation of ErbB2-containing heterodimers, even though they do not bind to ErbB 2 directly. It is contemplated that the inhibitory ligands work in a similar way, namely, one inhibitory ligand may exert an inhibitory activity towards more than one receptor, and more than one receptor combination, thus inhibiting ErbB-receptor mediated signaling (see also page 60 lines 29-31 of the application).

1.3. Drawings; Spec. (OA pp. 4-5)

The withdrawal of the prior objections to the drawings and specification, as well as certain rejections under 101 and 102(b), are gratefully acknowledged.

1.4. New Claims Objections (OA p. 6)

The objections to claims 8 and 9 are moot as those claims have been cancelled.

The objection to claims 1 and 4, on the ground that these claims cover non-elected inventions (i.e., sequences other than SEQ ID NO:81), is traversed on the grounds that the underlying restriction has been traversed. Generic claims reciting the common structure and activity are presented and allowable. See section 1.2 above.

The second objection to claim 1 is moot. We agree that "or 109-110" is informal. However, the correction is not to replace "or" with --and--, as suggested, as this would conflict with "any one" (note that the limitation is not formally in Markush group form), but rather to replace "or 109-110" with --109 or 110--, as has now been done.

2. Written Description Issues (OA pp. 7-11)

The examiner has rejected claims 1, 4, 6, 8-14, 32 and 41 as failing to comply with the written description requirement

and the enablement requirement of the first paragraph of 35 USC §112.

The Examiner has alleged that the specification does not provide adequate written description or teaching regarding the N-terminal flanking sequences preceding the first conserved cysteine of the EGF domain.

Claim 1 has been amended to recite "an isolated polypeptide comprising a splice variant of an ErbB ligand…. wherein the N-terminal sequence of the splice variant of an ErbB ligand preceding the first cysteine of the EGF domain is at least 90% homologous to the corresponding N-terminal sequence found in the known ErbB ligand from which the splice variant is derived…".

Claim 1 as amended refers to a polypeptide comprising a splice variant of an ErbB ligand, where the C-terminal portion of the variant contains a selected SEQ ID NO. (from the group of sequences specified in the claim), and the N-terminal portion of the variant contains a sequence having at least 90% homology to the corresponding N-terminal sequence found in the known (activating) ErbB ligand from which the splice variant is derived. The EGF domain of the variant (which is part of the C-terminal portion) is truncated - it ends one amino acid after the fourth conversed cysteine, which is also the penultimate amino acid of the polypeptide. The N-terminal flanking sequence of a certain splice variant are not derived from the N-terminal sequence of any known ErbB ligand, but rather from the specific known ligand from which that splice variant is derived.

The specification provides the accession numbers of the corresponding known ligands (please see page 65). A skilled artisan can readily find information about the sequences found

upstream to the first conserved cysteine of the EGF domain using these accession numbers.

Determination of conservative amino acid substitutions, that would maintain the properties of the splice variant, are within the capabilities of a skilled artisan, in particular in view of the guidance provided in page 18 lines 24-33 and in the paragraph bridging pages 24 and 25.

It is believed that a skilled artisan can envision the overall structure of the encompassed polypeptide and prepare it accordingly, and therefore the claims as amended meet the written description and enablement requirements of the first paragraph of 35 USC §112.

Respectfully submitted,

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